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Phosphazene high polymers are of interest as potential carrier molecules for transition metals and biologically active organic species. Small molecule phosphazene rings are models for the exploration of new synthetic methods that may be applicable to the high polymers. Five alternative routes have been developed for the linkage of transition metals to phosphazenes.

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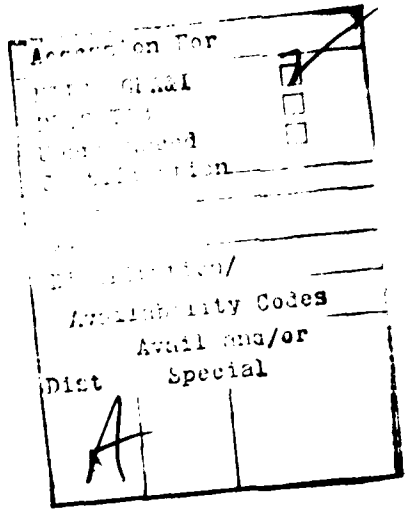

PHOSPHAZENE RINGS AND HIGH POLYMERS LINKED TO TRANSITION METALS OR BIOLOGICALLY ACTIVE ORGANIC SPECIES

by

H. R. Allcock

Prepared for publication in the ACS Symposium Series
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Department of Chemistry
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August 20, 1981

Phosphazene Rings and High Polymers Linked to Transition Metals or Biologically Active Organic Species

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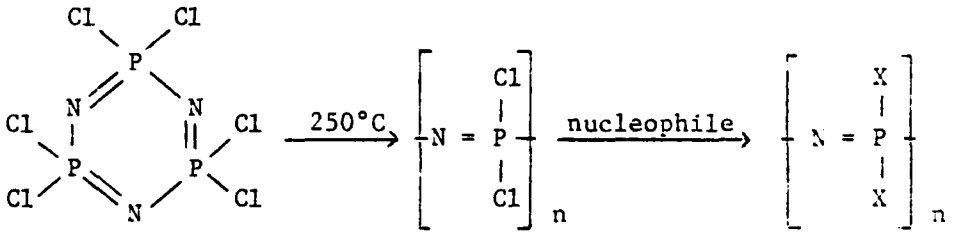
Macromolecules that contain phosphorus as a skeletal atom have been studied in detail for many years. Yet, compared to the vast array of known carbon-backbone polymers, macromolecules based on phosphorus have occupied only a small and very specialized niche. We have been systematically exploring the prospect that a broad new class of high polymers, the poly(organophosphazenes) (III), can be synthesized in which phosphorus rather than carbon plays a key role in the skeletal chain (1-3).



I II III

(n ≃ 15,000, X = OR, NR_2, alkyl, or aryl)

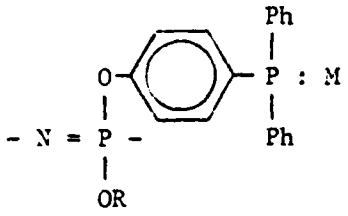
For most organic substituent groups, X, polymers of type III are hydrolytically stable and offer unusual combinations of physical and chemical properties not found in biological- or petrochemical-based macromolecules.

Two key principles have played a pivotal role in our exploration and development in this field. First, unlike most macromolecules, nearly all poly(organophosphazenes) are prepared by a substitutive technique, in which a broad range of different substituent groups are introduced via a reactive polymeric intermediate (II). Second, because substitution reactions play such an important role in the chemistry of these

polymers, and because the reactions of macromolecules are usually complex, we have made extensive use of species such as I as small molecule models for the reactions of II. Thus, the reactions of cyclic trimers and tetramers have been investigated in tandem with the reactions of the high polymers (4).

In this paper we consider two specific challenges. First, how might transition metals be linked to phosphazene high polymers? Such systems are of interest as immobilized catalysts or materials with unusual electrical properties. Second, how can bioactive agents be attached to polyphosphazenes to prepare, for example, targeted, slow release chemotherapeutic agents? An important link in this process would be the use of a carrier polymer that could biodegrade to harmless small molecules.

Five different approaches have been developed for the linkage of transition metals to cyclic or high polymeric phosphazenes. The first three make use of organic side groups as coordination ligands, the fourth utilizes the coordination power of the backbone nitrogen atoms, and the fifth involves the synthesis of derivatives in which the side group is itself an organometallic unit linked to the skeleton through phosphorus-metal bonds. These possibilities are illustrated in structures IV-VIII.



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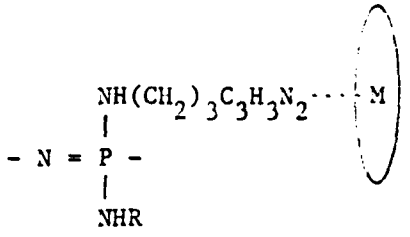

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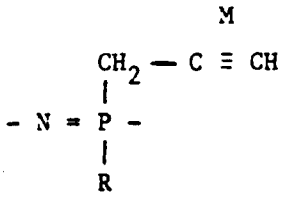

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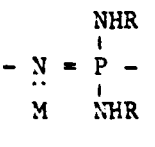

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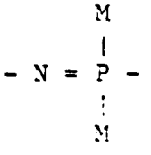
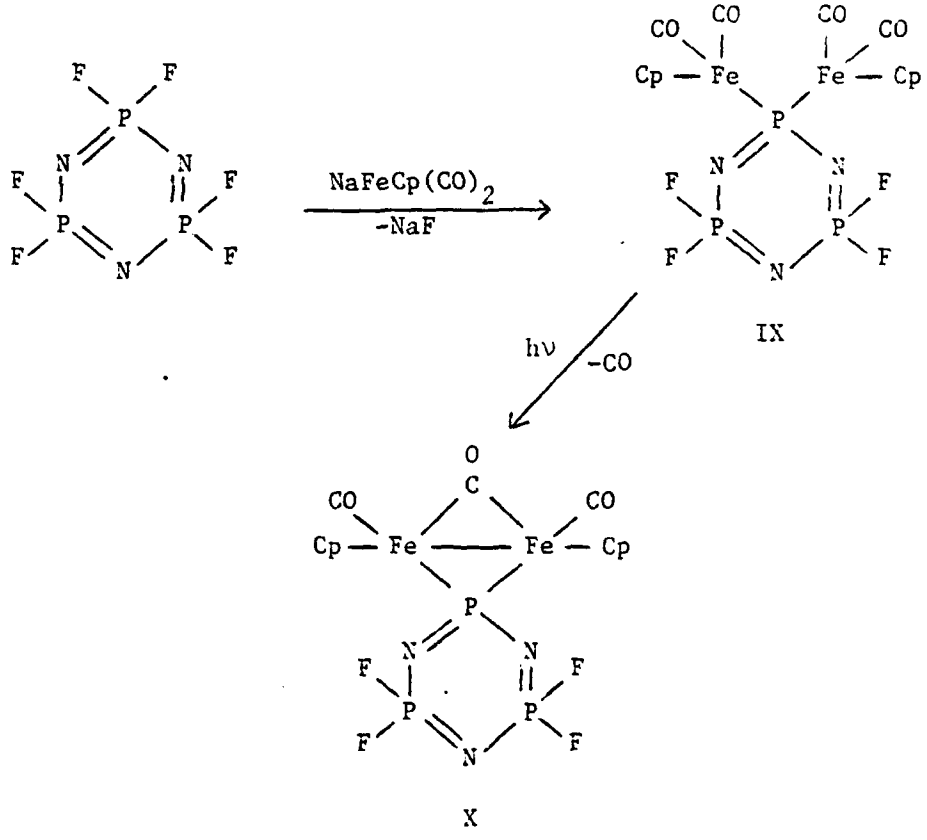


VIII

Species IV were prepared from p-bromophenoxy-substituted phosphazene trimers and high polymers, by metal-halogen exchange to yield the p-lithio-derivative, followed by reaction with diphenylchlorophosphine. Both cyclic trimers and high polymers containing the pendent phosphine reacted with $H_2Os(CO)_{10}$,

$MnCp(CO)_3$, AuCl, CuI, or $Rh_2Cl_2(CO)_4$ to yield the appropriate phosphazene-transition metal complex. The skeletal nitrogen atoms did not interfere with the process. On the other hand, it was shown earlier that $PtCl_2$ residues are bound strongly to the skeletal nitrogen atoms of $[NP(CH_3)_2]_4$, $[NP(NHCH_3)_2]_4$, and $[NP(NHCH_3)_2]_n$ (VII) (5). The latter compound is a prospective polymer-bound antitumor agent. The pendent imidazolyl derivative (V) coordinated strongly to heme or hemin in aqueous media (6) to yield products that are of interest both as heme-protein models and as redox systems. Our recent discovery of a facile route to the formation of propynyl phosphazenes via organocopper intermediates (7) has allowed the synthesis of pi-coordination derivatives of structure VI. The complex formed with $Co_2(CO)_8$ is especially stable.

The linkage of transition metals to skeletal phosphorus in a phosphazene has presented an unresolved challenge for many years. We have recently succeeded in the preparation of iron and ruthenium phosphazenes by the reaction shown below (8).



IX

X

An important feature of this approach is the isolation of species IX (as a yellow, crystalline solid) and, following mild photolysis, the red, metal-metal bonded product, IX. X-Ray crystal structures have been obtained for both compounds.

The linkage of steroid molecules to both cyclic and high polymeric phosphazenes has been studied (9). Steroids with hydroxyl groups at the 3-position can be converted to their sodium salts by treatment with sodium hydride. If the A-ring is aromatic, linkage of the steroid to the phosphazene skeleton occurs in a manner reminiscent of the behavior of simple aryloxides. However, if the A-ring is alicyclic, complex reactions occur, including dehydration of the A-ring by the phosphazene.

Two types of side group structures attached to a phosphazene ring or chain induce hydrolytic breakdown -- amino acid ester and imidazole residues. The former decompose to alcohol, amino acid, phosphate, and ammonia (10). Hexakis(imidazolyl)cyclotriphosphazene hydrolyzes rapidly in the pH range 6.5 to 7.8 by a mechanism that involves autocatalysis by the free imidazole liberated. Thus, either type of side group could facilitate biodegradation of chemotherapeutic carrier macromolecules.

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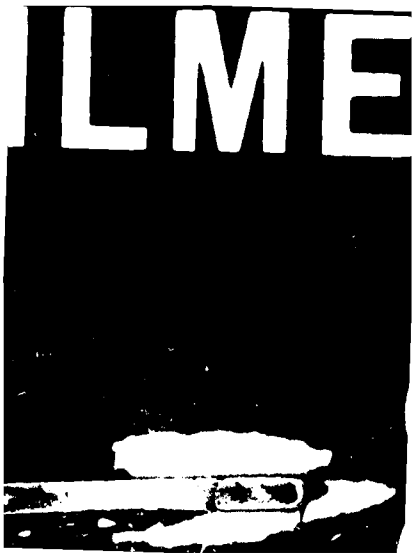
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